positions 98-117 of BMP-7 (SEQ ID NO: 21), the amino acid sequence at positions 320-340 (SEQ ID NO: 22), the amino acid sequence at positions 390-409 (SEQ ID NO: 23) and the amino acid sequence at positions 405-423 (SEQ ID NO: 24).

Should a more specific election be required, then Applicants respectfully elect the amino acid sequence at positions 293-313 of BMP-4 (SEQ ID NO: 14).

Part II – Bone graft material

Applicants were required to elect one of the bone graft materials in Claims 7 and 16. Applicants respectfully elect synthetic hydroxyapatite powders and porous blocks.

Part III - Crosslinkers

Applicants were required to elect one of the crosslinkers in Claims 9 and 22. Applicants respectfully elect succinimidyl-4-[N-maleimidomethylcyclohexane-1-carboxy-[6-amidocaproate](SMCC) and sulfo-SMCC.

Traversal of Election Requirement

Applicants respectfully traverse the election requirement for at least the following reasons.

The Examiner suggested that Claim 1 was anticipated by U.S. Patent No. 5,266,683, specifically, Column 64 of the '683 patent. Claim 1 is directed bone graft materials which have a cell adhesion-inducing peptide and/or tissue growth factor-derived peptide immobilized on the surface.

In this context, the term "immobilized" means that a peptide is tied to the surface of the material. For example, the invention can be understood with reference to paragraphs 29 and 30 of the published application, which are provided below for the Examiner's convenience.

> [0029] The peptides according to the present invention are not more sensitive to in vivo enzymatic reactions than the tissue growth factor itself and have a lower in vivo immunogenicity. When the active peptides are immobilized on the surface of bone graft materials, scaffolds, barrier

membranes or implants for tissue regeneration and used in surgical operations, the desired concentration of the active peptides can be locally present while showing activity, so that their therapeutic effects can be increased. Thus, the active peptides have suitable characteristics for the regeneration and repair of bone tissue and periodontal tissue.

[0030] The inventive peptides having free amino groups or cysteines at the N-terminal end are easy to immobilize on the surface of bone graft materials and scaffolds by crosslinkers. Crosslinkers suitable for use in the present invention include, but are not limited to, 1,4-bis-maleimidobutane (BMB), 1,11-bis-maleimido tetraethyleneglycol (BM[PEO].sub.4), 1-ethyl-3-[3-dimethyl aminopropyl]carbodiimide hydrochloride (EDC), succinimidyl-4-[N-maleimido methylcyclohexane-1-carboxy-[6-amidocaproate]] (SMCC) and sulfo-SMCC, succimidyl 6-[3-(2-pyridyldithio)-propionamido]hexanoate] (SPDP) and sulfo-SPDP), m-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) and sulfo-MBS, succimidyl [4-(p-maleimidophenyl)butyrate] (SMPB) and sulfo-SMPB. In addition, the peptides are chemically bound to the surface of bone graft materials and scaffolds so that they are immobilized on the surface in an amount of preferably 0.1-10 mg/cm^2, and more preferably 1-5 mg/cm^2.

In contrast, the '683 patent discloses matrix materials that have various proteins or polypeptides "associated with" them, or which have the proteins "disposed" or "dispersed" within them. The '683 patent does not disclose or suggest immobilizing the polypeptides or proteins on the surface of the matrix material.

In fact, the '683 patent teaches away from this concept. The '683 patent teaches that:

> Studies have shown that surface charge, particle size, the presence of mineral, and the methodology for combining matrix and osteogenic protein all play a role in achieving successful bone induction. **Perturbation of the charge by chemical modification abolishes the inductive response**. Particle size influences the quantitative response of new bone; particles between 70 .mu.m and 420 .mu.m elicit the maximum response. Contamination of the matrix with bone mineral will inhibit bone formation. Most importantly, the procedures used to formulate osteogenic protein onto the matrix are extremely sensitive to the physical and chemical state of both the osteogenic protein and the matrix.

(Section III of the '683 patent, entitled "Matrix Preparation," Emphasis added)

Thus, while the claimed invention relates to intentional modification of the surface, so that the therapeutic activity of the immobilized peptides is increased, the '683 patent teaches that chemically modifying the surface (which would be done if the peptides were immobilized on the surface) would abolish the inductive response that is taught as being required to grow bone. Therefore, since the claims require modification of the surface, and the '683 patent teaches that chemically modifying the surface abolishes activity, the '683 patent does not teach the invention, but rather, it teaches away from the invention.

Further, notwithstanding the fact that the subject matter of Claim 1 is neither disclosed nor suggested, it is clear that all members of the various families of peptides (i.e., all peptides derived from bone morphogenic protein) will function to enhance the growth of bone, so these are all inventively linked.

Still further, it would be unreasonable to limit claims to specific peptides, and specific agents to covalently immobilize the peptides to the surface of the material, and to specific materials. That is, even if the subject matter of Claim 1 were known in the art, which is not the case (at least with respect to the cited '683 patent), immobilization of a specific peptide would be patentable, regardless of the specific surface or coupling agent. Similarly, modification of the surface of a specific material, using peptides, generally, and/or using crosslinking agents, generally, would be patentable.

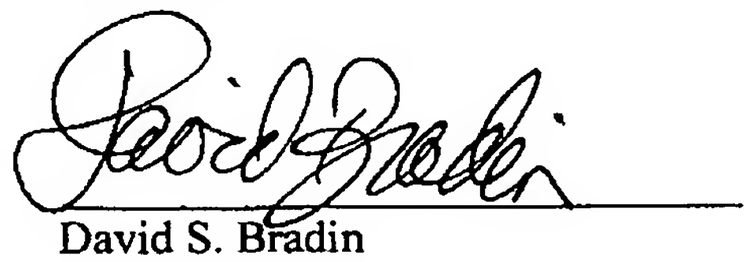
For at least these reasons, Applicants respectfully traverse the election requirement.

Notwithstanding the traversal, Applicants believe that the claims are in condition for examination on the merits, and, upon indication of allowability of a generic claim, Applicants understand that the Examiner will broaden the search to include more species than the ones elected in this Response to Election of Species Requirement.

4240-149

It is requested that examination and prosecution of this application proceed on the basis of the pending claims 1-22 in the application. If any questions remain, the Examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss same.

Respectfully submitted,



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